

EXPRESS MAIL CERTIFICATE

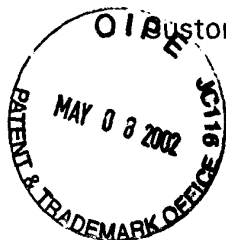
Date 5/9/02 Label No. E028647885-45

I hereby certify that, on the date indicated above, this paper or fee was deposited with the U.S. Postal Service & that it was addressed for delivery to the Assistant Commissioner for Patents, Washington, DC 20231 by "Express Mail Post Office to Addressee" service.

PLEASE CHARGE ANY DEFICIENCY UP TO \$300.00 OR CREDIT ANY EXCESS IN THE FEES DUE WITH THIS DOCUMENT TO OUR DEPOSIT ACCOUNT NO. 04-0100

B.W. LEE
Name (Print)

B.W. Lee
Signature



Customer No.:



07278

PATENT TRADEMARK OFFICE

Docket No.: 9373/1H812US3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Christopher A. Voigt, Zhen-Gang Wang, Frances H. Arnold, Stephen L. Mayo.

Serial No.: 10/016,668

Confirmation No.: 3843

Filed: October 26, 2001

For: GENE RECOMBINANT AND HYBRID PROTEIN DEVELOPMENT

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

Sir:

In order to comply with 37 CFR 1.97 and 1.98, attached hereto is a

copy of Form PTO-1449 and copies of the documents listed thereon.

In accordance with MPEP Sections 609 and 707.05(b), it is requested that each document cited (including any cited in applicant's specification which is not repeated on the attached Form PTO-1449) be given thorough consideration and that it be cited of record in the prosecution history of the present application by initialing Form PTO-1449 next to the document. Such initialing is requested even if the Examiner does not consider a cited document to be sufficiently pertinent to use in a rejection, or otherwise does not consider it to be prior art for any reason, or even if the Examiner does not believe that the guidelines for citation have been fully complied with. This is requested so that each document becomes listed on the face of the patent issuing on the present application.

The undersigned is also enclosing herewith a copy of a Partial Search Report issued for the PCT counterpart of the present patent application (Application No. PCT/US01/16831), in which the presently disclosed references were cited. Since a translation of the Partial Search Report is also enclosed, or the Partial Search Report utilizes conventional codes to characterize each cited reference, it is believed that the applicants in the above-identified patent application have now met the "concise explanation" requirement of 37 C.F.R. 1.98.

The present Supplemental Information Disclosure Statement is being submitted in compliance with 37 CFR 1.56, but the citation of such document is not to be construed as an admission that such document is necessarily relevant or

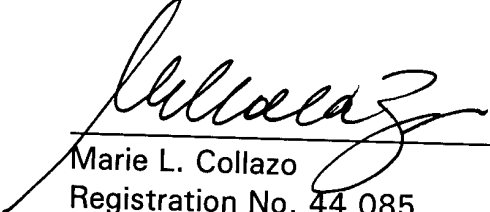
prior art. No representation is intended that the cited documents represent the results of a complete search, and it is anticipated that the Examiner, in the normal course of examination, will make an independent search and will determine the best prior art consistent with 37 CFR 1.104(a) and 1.106(b) and, in the course of each search, will review for relevance every document cited on the attached form even if not initialed.

It is believed that no fee is due. However, if the Commissioner determines that a fee is due, the Commissioner is hereby authorized to charge the above deposit account for any deficiency.

Early and favorable consideration is earnestly solicited.

Respectfully submitted,

Dated: May 7, 2002


Marie L. Collazo
Registration No. 44,085

DARBY & DARBY
Post Office Box 5257
New York, NY 10150-5257
(212) 527-7700

Serial No. 10/016,668

Docket No. 9373/1H812US3

**LIST OF REFERENCES CITED BY APPLICANT**

(Use Several Sheets if Necessary)

DOCKET NO.: 9373/1H812US3 SERIAL NO: 10/016,668
 APPLICANT: Zhen -Gang WANG et al. FILING DATE: 10/26/2001
 CONFIRMATION NO: 9136

U.S. PATENT DOCUMENTS

*EXAMINER INITIALS	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE
-----------------------	--------------------	------	------	-------	----------	-------------

FOREIGN PATENT DOCUMENTS

*EXAMINER INITIALS	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES NO
	1. 01/16810	03/08/01	WIPO	G06F	17/50	
	2. 01/61344	03/23/01	WIPO	G01N	33/48	
	3. 98/41623	09/24/98	WIPO	C12N	15/10	
	4. 00/09755	02/24/00	WIPO	C12Q	1/68	
	5. 00/18906	04/06/00	WIPO	C12N	15/10	

OTHER REFERENCES**(INCLUDING AUTHOR, TITLE DATE, PERTINENT PAGES, ETC.)**

*EXAMINER
INITIALS

6. Chang et al., "Evolution of a cytokine using DNA family shuffling," *Nature Biotechnology*, 1999, 17:793-797.
7. Crameri et al., "Construction and evolution of antibody-phage libraries by DNA shuffling," *Nature Medicine*, 1996, 2:100-102.
8. Dahiyat et al., "Protein design automation," *Protein Science*, 1996, 5:895-903.
9. Holm et al., "Parser for Protein Folding Units," *Proteins: Structure, Function, and Genetics*, 1994, 19:256-268.
10. Niggeman et al., "Exploring Local and Non-local Interactions for Protein Stability by Structural Motif Engineering," *J. Mol. Biol.*, 2000, 296:181-195.
11. Voigt et al., "Computational method to reduce the search space for directed protein evolution," *PNAS*, 2001, 98:3778-3783.
12. Voigt et al., "Computationally Focusing the Directed Evolution of Proteins," *Journal of Cellular Biochemistry Supplement*, 2001, 37:58-63.
13. Voigt et al., "Trading Accuracy for Speed: A Quantitative Comparison of Search Algorithms in Protein Sequence Design," *J. Mol. Biol.*, 2000, 299:789-803.

**LIST OF REFERENCES CITED BY APPLICANT**

(Use Several Sheets if Necessary)

DOCKET NO.: 9373/1H812US2 SERIAL NO: 09/863,765
APPLICANT: Zhen -Gang WANG et al. FILING DATE: 05/23/2001
CONFIRMATION NO: 9136

*EXAMINER
INITIALS

14. Vose et al., "Schema Disruption," 1991, 237-242.

EXAMINER: _____

DATE CONSIDERED: _____

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1. The present communication is an Annex to the invitation to pay additional fees (Form PCT/ISA/206). It shows the results of the international search established on the parts of the international application which relate to the invention first mentioned in claims Nos.:
- see 'Invitation to pay additional fees'**
2. This communication is not the international search report which will be established according to Article 18 and Rule 43.
3. If the applicant does not pay any additional search fees, the information appearing in this communication will be considered as the result of the international search and will be included as such in the international search report.
4. If the applicant pays additional fees, the international search report will contain both the information appearing in this communication and the results of the international search on other parts of the international application for which such fees will have been paid.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BOGARAD LEONARD D ET AL: "A hierarchical approach to protein molecular evolution." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 96, no. 6, 16 March 1999 (1999-03-16), pages 2591-2595, XP002193260 March 16, 1999 ISSN: 0027-8424 cited in the application the whole document <div align="center">---</div>	
A	CAMERI A ET AL: "Construction and evolution of antibody-phage libraries by DNA shuffling" NATURE MEDICINE, NATURE PUBLISHING, CO, US, vol. 2, no. 1, January 1996 (1996-01), pages 100-102, XP002098467 ISSN: 1078-8956 the whole document <div align="center">---</div>	
A	DAHIYAT B I ET AL: "PROTEIN DESIGN AUTOMATION" PROTEIN SCIENCE, CAMBRIDGE UNIVERSITY PRESS, CAMBRIDGE, GB, vol. 5, no. 5, 1 May 1996 (1996-05-01), pages 895-903, XP002073372 ISSN: 0961-8368 the whole document <div align="center">---</div>	

-/--

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>STREET ARTHUR G ET AL: "Computational protein design." STRUCTURE (LONDON), vol. 7, no. 5, May 1999 (1999-05), pages R105-R109, XP002193261 ISSN: 0969-2126 the whole document</p> <p>---</p>	
A	<p>NIGGEMANN MONIKA ET AL: "Exploring local and non-local interactions for protein stability by structural motif engineering." JOURNAL OF MOLECULAR BIOLOGY., vol. 296, no. 1, 11 February 2000 (2000-02-11), pages 181-195, XP002193262 ISSN: 0022-2836 the whole document</p> <p>---</p>	
A	<p>WO 98 41623 A (NOVONORDISK AS) 24 September 1998 (1998-09-24) the whole document</p> <p>---</p>	
A	<p>WO 00 09755 A (PANGENE CORP) 24 February 2000 (2000-02-24) the whole document</p> <p>---</p>	
A	<p>WO 00 18906 A (MAXYGEN INC ;LIU LU (US); PATTEN PHILLIP A (US); STEMMER WILLEM P) 6 April 2000 (2000-04-06) the whole document</p> <p>---</p>	
A	<p>HOLM LIISA ET AL: "Parser for protein folding units." PROTEINS STRUCTURE FUNCTION AND GENETICS, vol. 19, no. 3, 1994, pages 256-268, XP001064311 ISSN: 0887-3585 abstract page 268, left-hand column, last paragraph</p> <p>---</p>	
A	<p>VOSE, M.D. AND LIEPENS, G.E.: "Schema disruption" 1991, MORGAN KAUFFMAN, SAN MATEO, CA, USA XP001064313 In: Belew R.K. and Booker, L.B. (Eds). "Proceedings of the fourth international conference on genetic algorithms", pages 237-242.</p> <p>---</p>	
	<p>---</p> <p>-/--</p>	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	VOIGT C A ET AL: "TRADING ACCURACY FOR SPEED: A QUANTITATIVE COMPARISON OF SEARCH ALGORITHMS IN PROTEIN SEQUENCE DESIGN" JOURNAL OF MOLECULAR BIOLOGY, LONDON, GB, vol. 299, no. 3, 2000, pages 789-803, XP001061223 ISSN: 0022-2836 the whole document	
A	--- CHANG C-C J ET AL: "EVOLUTION OF A CYTOKINE USING DNA FAMILY SHUFFELING" NATURE BIOTECHNOLOGY, NATURE PUBLISHING, US, vol. 17, no. 8, August 1999 (1999-08), pages 793-797, XP000946490 ISSN: 1087-0156 the whole document	19
P,X	--- VOIGT CHRISTOPHER A ET AL: "Computational method to reduce the search space for directed protein evolution." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 98, no. 7, 27 March 2001 (2001-03-27), pages 3778-3783, XP002193263 March 27, 2001 ISSN: 0027-8424 the whole document	1-18,23, 28-33, 36,37
T	--- VOIGT C A ; MAYO S L ; ARNOLD F H ; WANG Z: "Computationally focusing the directed evolution of proteins. " JOURNAL OF CELLULAR BIOCHEMISTRY - SUPPLEMENT, vol. 37, 29 January 2002 (2002-01-29), pages 58-63, XP002193264 page 61, left-hand column, paragraph 2 -page 62	
T	--- WO 01 16810 A (EUROP MOLECULAR BIOLOGY LAB ;SERRANO LUIS (DE); LACROIX EMMANUEL ()) 8 March 2001 (2001-03-08) the whole document	
T	--- WO 01 61344 A (VOIGT CHRISTOPHER ;MAYO STEPHEN L (US); WANG ZHEN GANG (US); ARNOLD) 23 August 2001 (2001-08-23) the whole document -----	

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9841623	A	24-09-1998	AU 738461 B2	20-09-2001
			AU 6611698 A	12-10-1998
			WO 9841623 A1	24-09-1998
			EP 1015575 A1	05-07-2000
			JP 2001516216 T	25-09-2001
			US 6291165 B1	18-09-2001
WO 0009755	A	24-02-2000	US 6074853 A	13-06-2000
			AU 5774899 A	06-03-2000
			EP 1105472 A2	13-06-2001
			WO 0009755 A2	24-02-2000
WO 0018906	A	06-04-2000	AU 1199000 A	17-04-2000
			EP 1117777 A2	25-07-2001
			WO 0018906 A2	06-04-2000
			AU 2415200 A	01-08-2000
			AU 3210100 A	01-08-2000
			AU 3210200 A	01-08-2000
			EP 1151409 A1	07-11-2001
			EP 1062614 A1	27-12-2000
			EP 1072010 A2	31-01-2001
			EP 1130093 A1	05-09-2001
			EP 1108783 A2	20-06-2001
			EP 1108781 A2	20-06-2001
			WO 0042559 A1	20-07-2000
			WO 0042560 A2	20-07-2000
			WO 0042561 A2	20-07-2000
			US 6319714 B1	20-11-2001
WO 0116810	A	08-03-2001	AU 1132001 A	26-03-2001
			WO 0116810 A2	08-03-2001
WO 0161344	A	23-08-2001	AU 3839701 A	27-08-2001
			WO 0161344 A1	23-08-2001
			US 2001051855 A1	13-12-2001